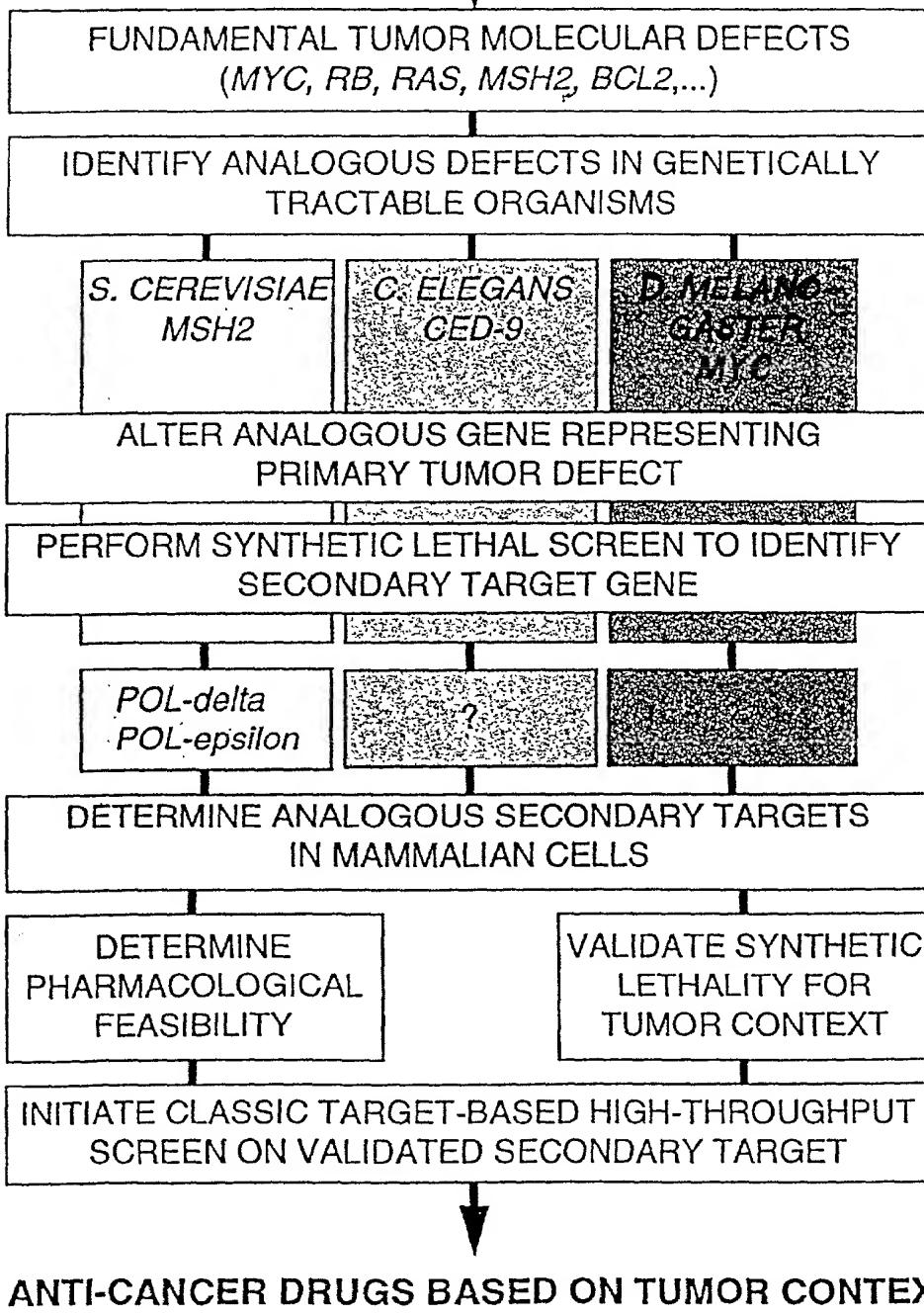


FIGURE 1

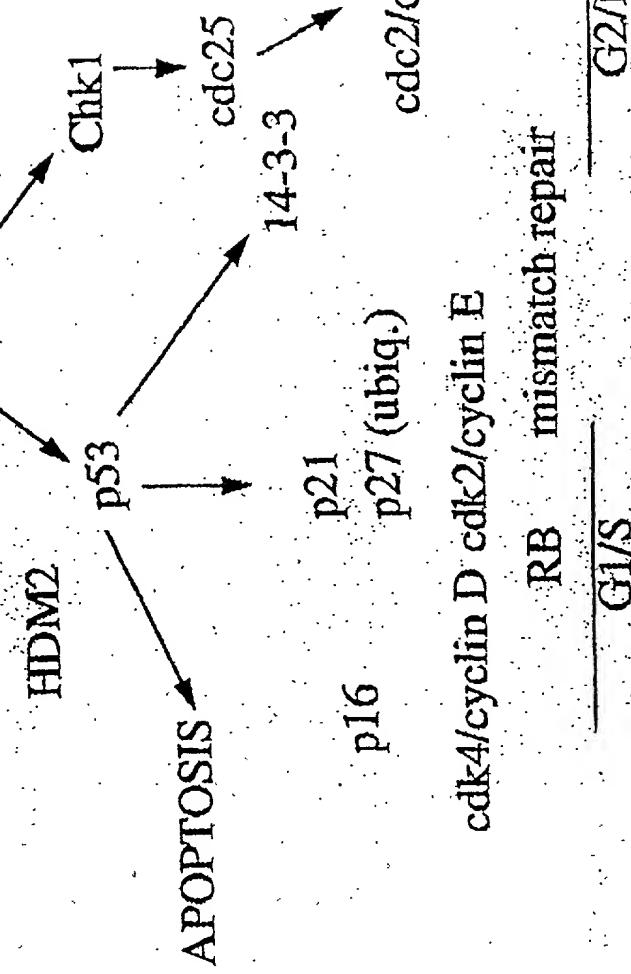
MOLECULAR ALTERATIONS IN TUMORS



Cell Cycle/DNA Damage Response Pathways

DNA Damage

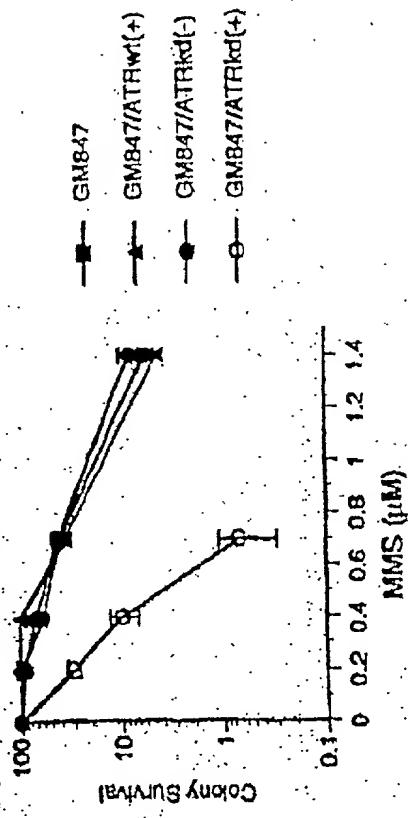
PIK-domain proteins (ATM, ATR, DNA-PK)



MAMMALIAN CELL EVALUATION OF ATR AS A TARGET

1. Overexpression of ATR-KD not tolerated in human tumor cell lines (MCF-7, A549)

2. Inducible ATR-KD sensitizes cells to DNA damaging agents



3. LCK promoter driven ATR-KD transgenic mice have cells stably expressing ATR-KD in thymus

Figure 4

Synthetic lethality:

- Use primary defect as a selective context to kill tumor cells with an alteration in gene A.
- Combined defects in gene A and gene B kill tumor cells while disrupting gene B activity alone has no effect on normal cells.

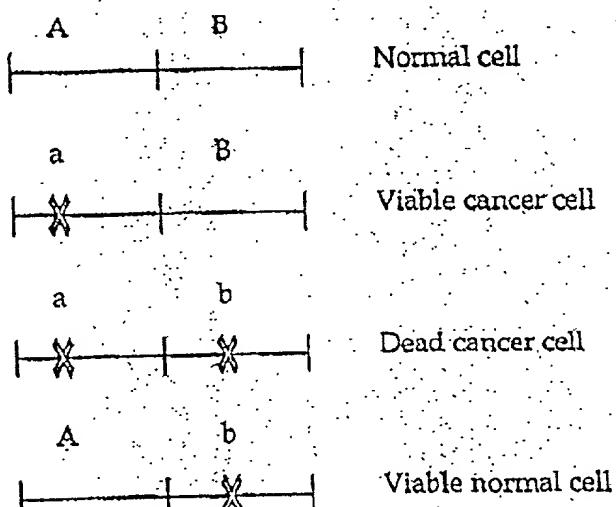


Figure 5

Human genes altered in tumors and their relatives in model genetic systems. Genes that are not structural homologs but act in analogous pathways (such as human *p53* and *S. cerevisiae RAD9*) are shown in brackets. *Saccharomyces cerevisiae* genes are designated with superscript Sc, *S. pombe* with Sp, *C. elegans* with Ce, and *D. melanogaster* with Dm. Because of space limitations, this is only a representative list of genes mutated in tumors that have genetic analogs in model systems.

Function	Human genes	Model system analogs: structural homologs or related biological roles
DNA damage checkpoint	<i>p53</i>	[<i>RAD9</i> ^{Sc} , <i>rad1</i> - ^{Sp}]
	ATM	<i>MEC1</i> ^{Sc} , <i>TEL1</i> ^{Sc} , <i>rad3</i> ^{3+Sp} , <i>mei-41</i> ^{Dm}
DNA mismatch repair	<i>MSH2</i> , <i>MLH1</i>	<i>MSH2</i> ^{Sc} , <i>MLH1</i> ^{Sc}
Nucleotide excision repair	<i>XP-A</i> , <i>XP-B</i>	<i>RAD14</i> ^{Sc} , <i>RAD25</i> ^{Sc}
O ⁶ -methylguanine reversal	<i>MGMT</i>	<i>MGT1</i> ^{Sc}
Double-strand break repair	<i>BRCA2</i> , <i>BRCA1</i>	[<i>RAD51</i> ^{Sc} , <i>RAD54</i> ^{Sc}]
DNA helicase	<i>BLM</i>	<i>SGS1</i> ^{Sc} , <i>rqh1</i> - ^{Sp}
Growth factor signaling	<i>RAS</i>	<i>RAS1</i> ^{Sc} , <i>RAS2</i> ^{Sc} , <i>let-60</i> ^{Ce}
Cell cycle control	<i>NF1</i> <i>MYC</i> <i>PTH</i> Cyclin D, Cyclin E <i>P27</i> ^{kip1} <i>Rb</i>	<i>IRA1</i> ^{Sc} , <i>IRA2</i> ^{Sc} <i>dMyc</i> ^{Dm} <i>patched</i> ^{Dm} <i>CLN1</i> ^{Sc} , <i>CLN2</i> ^{Sc} , Cyclin D ^{Dm} , Cyclin E ^{Dm} [<i>SIC1</i> ^{Sc}] <i>Rbf</i> ^{Dm}
Apoptosis	<i>BCL-2</i>	<i>ced-9</i> ^{Ce}

Cell Cycle/DNA Damage Response Pathways

DNA Damage



PIK-domain proteins (ATM, ATR, DNA-PK)

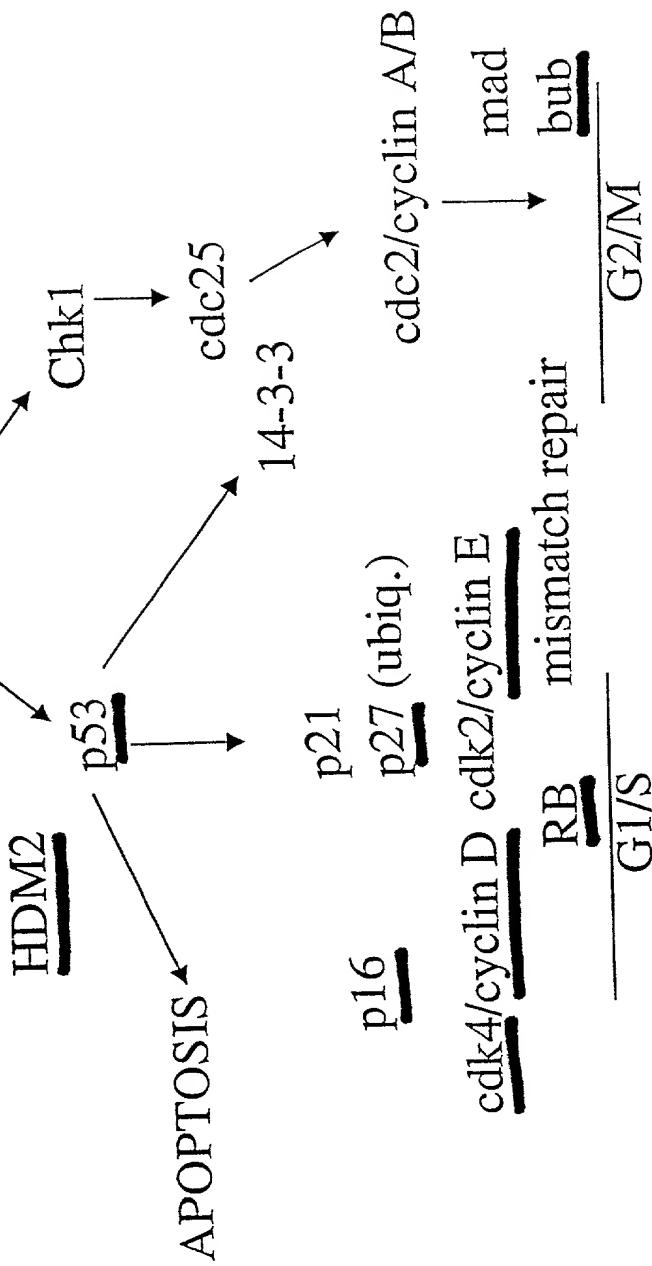


Figure 6

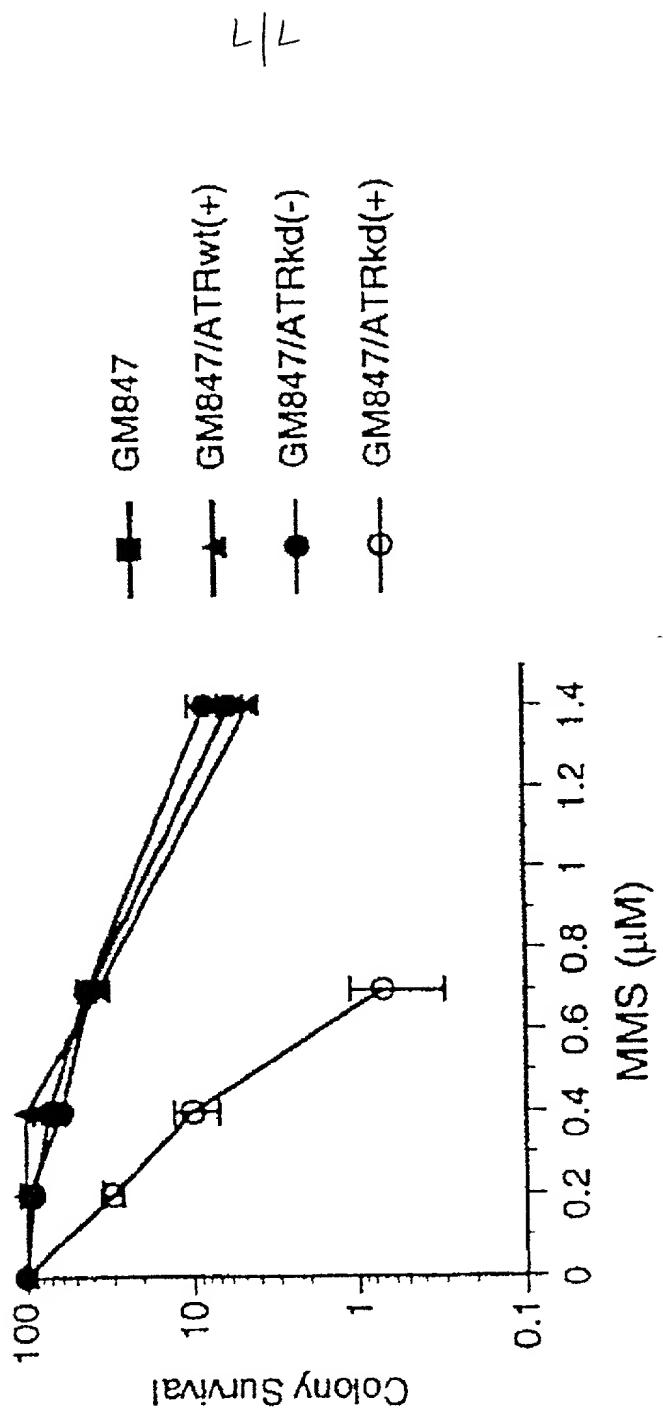


Figure 7